PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|---|---|
| In re Reissue Application of : | U.S. Patent No. 6,001,844 | | |
| Applicants: | Bakshi et al. | | |
| Reissue Serial No.: | To Be Assigned | Case No.: 19526PR | Art Unit: To be Assigned |
| Filed: | December 14, 2001 | | Examiner: To be Assigned |
| For: | 4-AZASTEROIDS FOR TREATMENT OF HYPERANDROGENIC CONDITIONS | | |

EXPRESS MAIL CERTIFICATE
DATE OF DEPOSIT December 14 2001
EXPRESS MAIL NO. EL523908486US
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" BEFORE 5 P.M. ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231.
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DATE 12-14-01

**BOX REISSUE**
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

The preliminary amendment is being sent concurrently with a request for reissue of the above-identified patent. Claims 1 to 13 are the granted claims of US 6,001,844 (the '844 Patent) here sought to be reissued. Prior to examination of this reissue application, please amend the Specification and Claims as follows.

IN THE SPECIFICATION

Replace the paragraph beginning at column 5, line 15, with the following:

Combinations of substituents and/or variables are [pennissible]permissible only if such combinations result in stable compounds.

Replace the paragraph beginning at column 8, line 42, with the following:

The daily dosage of the products may be varied over a range from 0.01 to 1,000 mg per adult human/per day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 [mgas/g] mg/kg of body weight per day. The range is more particularly from about 0.001 [msg/kg] mg/kg to 7 mg/kg of body weight per day.

Replace the paragraph beginning at column 16, line 34, with the following:

To mixture of N-(diphenylmethyl)-4-methyl-3-oxo-4-axa-5α-androst-1-ene-17-β-carboxamide (obtain via the procedures of Example 8, 100 mg, 0.20 mmoles), sodium hydride (8.8 mg, 0.22 mmoles) and tetrahydrofuran (2.0 mL) was added [jodomethane] iodomethane (0.0138 mL, 0.22 mmoles). The reaction was stirred overnight. The reaction was quenched with water and the solvent was evaporated *in vacuo*. The residue was dissolved in methylene chloride (75 mL) and washed with water (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate and filtered. The solvent was evaporated *in vacuo* to give a yellow/white foam. The crude foam was chromatographed on preparative TLC plates ($SiO_2$) using 1:9 acetone: methylene chloride as the mobile phase to yield the titled compound as a white foam. TLC rf = 0.6, 1:9 acetone:methylene chloride.

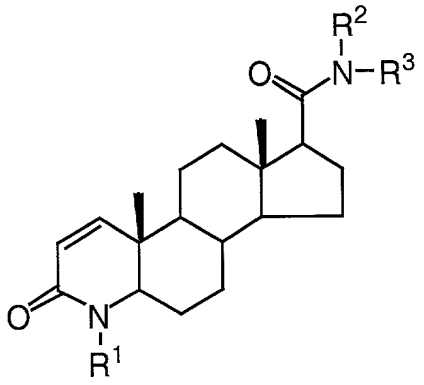
Replace the paragraph beginning at column 20, line 60, with the following:

In these clinical [photographss] photographs, the only variable allowed is the global area's appearance. Anything extraneous to the area (clothing, furniture, walls, etc.) is eliminated from the fields to be photographed.

IN THE CLAIMS:

Cancel Claims 2, 3, and 6 to 10.

1. (Amended) A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt or ester thereof, wherein:

$R^1$ is methyl;

$R^2$ is [selected from:]

[(a) ]H[, and]

[(b) $C_{1-6}$ alkyl];

$R^3$ is selected from:

(a) heteroaryl, either unsubstituted or substituted with one to three substituents independently selected from:

(1) halo (F, Cl, Br, I),

(2) $C_{1-2}$ alkyl[;],

(3) trifluoromethyl,

(4) nitro,
(5) hydroxy,
(6) cyano,
(7) amino,
(8) $C_{1-2}$ alkyloxy,
(9) phenyl, and
(10) heteroaryl; and

(b) phenyl substituted with one to three substituents independently selected from:
(1) halo (F, Cl, Br, I),
(2) $C_{1-2}$ alkyl;
(3) trifluoromethyl,
(4) nitro,
(5) hydroxy,
(6) phenyl,
(7) $C_{1-2}$ alkyloxy,
(8) heteroaryl,
(9) $S(O)_nR^4$, wherein n is selected from 0, 1, and 2, and
(10) alkyoxy;

$R^4$ is selected from:
(a) $C_{1-4}$ alkyl,
(b) phenyl, and
(c) heteroaryl.

4. (Amended) The compound according to claim [3] 1 wherein: heteroaryl is selected from:
(a) pyridyl,
(b) pyrizinyl,
(c) pyrazolyl, and

(d) thiazolyl;

either unsubstituted or substituted with one to three substituents independently selected from:

(1) halo (F, Cl, Br, I),
(2) $C_{1-2}$ alkyl,
(3) trifluoromethyl,
(4) nitro,
(5) hydroxy,
(6) cyano,
(7) amino, and
(8) $C_{1-2}$ alkyloxy[.]; and

phenyl is substituted with one to three substituents independently selected from:

(1) halo (F, Cl, Br, I),
(2) $C_{1-2}$ alkyl;
(3) trifluoromethyl,
(4) nitro,
(5) hydroxy,
(6) phenyl, and
(7) $C_{1-2}$ alkyloxy.

5. (Amended) The compound according to claim [3] 1 selected from:

(a) N-(4-pyridyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,
(b) N-(3-pyridyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,
(c) N-(pyrazinyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,
(d) N-(3-pyrazoyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide, [and]
(e) N-(2-thiazolyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide[.] ,

(f) N-(2-methylphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(g) N-(2-methoxyphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(h) N-(2-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(i) N-(4-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(j) N-(2-fluorophenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(k) N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(l) N-(2,5-bistrifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,N-(2-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide, and

(n) N-(4-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

13. (Amended) The composition according to claim 11 wherein the compound is selected from:

(a) N-(4-pyridyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,

(b) N-(3-pyridyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,

(c) N-(pyrazinyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,

(d) N-(3-pyrazoyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide, [and]

(e) N-(2-thiazolyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide[.] ,

(f) N-(2-methylphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(g) N-(2-methoxyphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(h) N-(2-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(i) N-(4-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(j) N-(2-fluorophenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(k) N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(l) N-(2,5-bistrifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,N-(2-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide, and

(n) N-(4-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

14. The compound according to Claim 1, or a pharmaceutically acceptable salt or ester thereof, wherein:

$R^1$ is methyl;

$R^2$ is H;

$R^3$ is: heteroaryl, either unsubstituted or substituted with one to three substituents independently selected from:

(1) halo (F, Cl, Br, I),

(2) $C_{1-2}$ alkyl;

(3) trifluoromethyl,

(4) nitro,

(5) hydroxy,

(6) cyano,

(7) amino,

(8) $C_{1-2}$ alkyloxy,

(9) phenyl, and
(10) heteroaryl.

15. The compound according to Claim 14, or a pharmaceutically acceptable salt or ester thereof, wherein:

$R^1$ is methyl;

$R^2$ is H;

$R^3$ is: heteroaryl, selected from:
(a) pyridyl,
(b) pyrazinyl,
(c) pyrazolyl, and
(d) thiazolyl,
either unsubstituted or substituted with one to three substituents independently selected from:
(1) halo (F, Cl, Br, I),
(2) $C_{1-2}$ alkyl;
(3) trifluoromethyl,
(4) nitro,
(5) hydroxy,
(6) cyano,
(7) amino, and
(8) $C_{1-2}$ alkyloxy.

16. The compound according to Claim 15 which is:
(a) N-(4-pyridyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,
(b) N-(3-pyridyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide, (c) N-(pyrazinyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide,
(d) N-(3-pyrazoyl)-3-oxo-4-methyl-4-aza-5α-androst-1-ene-17β-carboxamide, and

(e) N-(2-thiazolyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

17. The compound according to Claim 1, or a pharmaceutically acceptable salt or ester thereof, wherein:

$R^1$ is methyl;

$R^2$ is H;

$R^3$ is phenyl substituted with one to three substituents independently selected from:

(1) halo (F, Cl, Br, I),
(2) $C_{1-2}$ alkyl;
(3) trifluoromethyl,
(4) nitro,
(5) hydroxy,
(6) phenyl,
(7) $C_{1-2}$ alkyloxy,
(8) heteroaryl,
(9) $S(O)_nR^4$, wherein n is selected from 0, 1, and 2, and
(10) alkyoxy; and

$R^4$ is selected from:

(a) $C_{1-4}$ alkyl,
(b) phenyl, and
(c) heteroaryl.

18. The compound according to Claim 17 wherein:

$R^1$ is methyl;
$R^2$ is H;

$R^3$ is phenyl substituted with one to three substituents independently selected from:

(1) halo (F, Cl, Br, I),
(2) $C_{1-2}$ alkyl;
(3) trifluoromethyl,
(4) nitro,
(5) hydroxy,
(6) phenyl, and
(7) $C_{1-2}$ alkyloxy.

19. The compound according to Claim 18 selected from:

(a) N-(2-methylphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,
(b) N-(2-methoxyphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,
(c) N-(2-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,
(d) N-(4-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,
(e) N-(2-fluorophenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,
(f) N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,
(g) N-(2,5-bistrifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,(h) N-(2-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide, and
(i) N-(4-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

20. The compound according to Claim 18, wherein:

$R^1$ is methyl;
$R^2$ is H;
$R^3$ is phenyl substituted with one substituent independently selected from:

(1) halo (F, Cl, Br, I), and

(2) trifluoromethyl.

21. The compound according to Claim 19, selected from:

(a) N-(2-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(b) N-(2-fluorophenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide, and

(c) N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

22. N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

23. The composition according to Claim 11 wherein the compound is selected from:

(a) N-(2-methylphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(b) N-(2-methoxyphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(c) N-(2-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(d) N-(4-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(e) N-(2-fluorophenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(f) N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,

(g) N-(2,5-bistrifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide,(h) N-(2-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide, and

(i) N-(4-biphenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

24. The composition according to Claim 23 wherein the compound is selected from:

(a) N-(2-chlorophenyl)-3-oxo-4-aza-4-methyl-5α-androst -1-ene-17β-carboxamide,

(b) N-(2-fluorophenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide, and

(c) N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

25. The composition according to Claim 24 wherein the compound is N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5α-androst-1-ene-17β-carboxamide.

REMARKS

The '844 patent issued December 14, 1999, on Application Serial No. 09/029,926 ("the '926 application") filed March 11, 1998, as the national phase application under 35 U.S.C. 371 of PCT Application Serial No. PCT/US96/14564, filed September 11, 1996, based on U.S. Provisional Application Serial No. 60/003,826, filed September 15, 1995.

Claims 1 through 13 were granted in the '844 patent. Claims 2, 3 and 6 to 10 3 have been canceled. Claims 1,4, 5, 9, 10, 13 have been amended, and new Claims 14 through 25 have been added. Currently, Claims 1, 4 , 5 and 11 through 25 are pending in the present application.

Claim 1 has been amended to select a single element from the Markush group for $R^1$ and $R^2$. $R^1$ is now methyl, as specified in originally issued Claim 2. $R^2$ has been amended to be hydrogen ("H"), as specified in originally issued Claim 3. In addition, Claim 1 has been amended to add $R^3$ as substituted phenyl, as supported by the specification of the issued patent at column 4, lines 38-51.

Claims 4 and 5, which originally depended on Claim 3, have been amended to depend on amended Claim 1, which incorporates all of the limitations of originally issued Claim 3.

In addition, Claim 4 has been amended to add $R^3$ as substituted phenyl, as supported by the specification of the issued patent at column lines 45 to 60, in particular lines 45-52, 54, 55, and 60.

Claims 5 and 13 have been amended to add species wherein $R^3$ is substituted phenyl, as supported by the specification of the issued patent at column 5, line 64 through column 6, line 15.

New Claims 14 through 16 are directed to compounds wherein $R^3$ is heteroaryl, either unsubstituted or substituted. In these claims, $R^1$ is supported by originally issued Claim 2 in the '844 patent, and the specification at column 5, line 60; $R^2$ is supported by originally issued Claim 3 in the '844 patent. In Claim 14, $R^3$ and $R^4$ are supported by originally issued Claim 1 in the '844 patent, and the specification at column 4, lines 38-51, and column 5, lines 11-14. In Claim 15, $R^3$ is supported by originally issued Claim 4 in the '844 patent. Claim 16 finds support in originally issued Claim 5 in the '844 patent.

New Claim 17 finds support throughout the specification, for example at column 5, lines 45 to 60.

New Claim 18 finds support in the specification at column 5, lines 45 to 60, in particular lines 45-52, 54, 55, and 60.

New Claim 19 finds support in the specification at column 5, line 64 through column 6, line 15.

New Claim 20 finds support in column 4, lines 38-51, in particular, lines 38-40 and 42.

New Claim 21 finds support in the specification as Examples 3, 4, and 6, appearing in column 15 as the second, third, and fifth entry in the table, as well as in column 6, lines 1, 2, 5-8.

New Claim 22 finds support in the specification as Example 4, appearing in column 15 as the third entry in the table, and in column 6, lines 7-8.

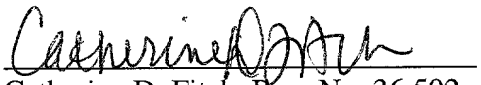
New Claim 23 to 26 find support in originally issued Claim 11 of the '844 patent. In addition, Claim 23 finds support in the specification at column 5, line 64 through column 6, line 15. Claim 24 finds support in the specification as Examples 3, 4, and 6, appearing in column 15 as the second, third, and fifth entry in the table, as well as in column 6, lines 1, 2, 5-8. Claim 24 finds additional support in the specification as Example 4, appearing in column 15 as the third entry in the table, and in column 6, lines 7-8.

The specification has been amended to correct minor typographical errors. In particular, in the paragraph beginning at column 5, line 15, "pennissible" has been corrected to read –permissible--; in the paragraph beginning at column 8, line 42, both "mgas/g" and "msg/kg" have been corrected to read --mg/kg--; in the paragraph beginning at column 16, line 34, "jodomethane" has been corrected to read –iodomethane--; and in the paragraph beginning at column 20, line 60, "photographss" has been corrected to read –photographs--.

The amendments above to the specification and claims do not add new matter to the present reissue application.

Applicants respectfully submit that the submitted claims are proper, and their allowance in this reissue application is respectfully requested.

Respectfully submitted,

By 

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